Comparative Analysis of p53 Protein Expression in Early-onset and Later-onset Colorectal Cancers

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Abstract:

Background: The global incidence of early onset colorectal cancer (CRC) is rapidly rising. However the reason for this and genomic characteristics of early onset CRC is largely unknown. p53 mutation is common in CRC and has been linked to an increased risk of early onset CRC.

Materials & Methods: All CRC patients operated at Department of Surgical Oncology, NICRH, between October 1, 2021 and September 30, 2022 were included in this study. Demographic and clinical data and surgical findings were recorded. Histopathology and p53 immunohistochemistry (IHC) analysis was done. Patients were categorized in two groups – 'Early onset' (diagnosed before 50 years of age) and 'Late onset' (diagnosed at or after 50 years of age). p53 protein IHC status (Mutant or Wild type) and other clinicopathological features were compared between the two groups.

Result: Out of 129 patients operated, 75 (58.14%) patients were in the early onset group. Compared to the late onset group, early onset patients had longer duration of symptoms (112.4 days vs. 88.7 days; p = .032), more peritoneal seedlings during surgery (14.7% vs. 1.9%, p = .011), and more poor differentiation (p = .062) and higher grades (p = .017) on histopathological analysis. Early onset patients had significantly more p53 mutation on IHC analysis than elderly ones (34.7% vs. 16.7%, p = .018). Age of onset showed no significance on either disease free survival (DFS) or overall survival (OS) in this study. On comparison of patients with either mutant (MT) or wild type (WT) p53 protein, those with MTp53 had more positive family history (20.0% vs. 3.2%, p=.004), higher levels of CEA (6.4 vs. 4.3, p = .028), higher pathological stage (p = .029), more chance of disease progression or recurrence during follow up (p=.035). Short term survival analysis showed patients with p53 mutation had significantly less DFS (p < .001) and OS (p = .001).

Conclusion: Early onset CRC was more prevalent in this study, and was associated with significantly more p53 mutation than the elderly patients. The clinical application of p53 mutation analysis by IHC in all CRC cases, particularly in the early onset patients, should be evaluated.

Key words: colorectal cancer, early onset, p53 mutation

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Introduction:

Colorectal cancer (CRC) is the third most commonly diagnosed cancer worldwide, with an estimated 1.88 million new cases in 2020.[1] Over the past several decades, the incidence of early-onset colorectal cancer (EOCRC; in patients <50 years old) has increased at an alarming rate. This rise of incidence as well as mortality of EOCRC is global.[2][3][4] TP53 mutations, but not p53 positive immunohistochemistry (IHC), have been consistently associated with poor prognosis in several types of cancers, including colorectal cancers.[5][6] Kim and colleagues found higher frequency of TP53 mutation

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and comparatively lower frequency of APC and KRAS mutation in early onset CRC.[7] It has been observed that early onset cancers tend to be more aggressive, and often associated with unfavorable histologic variants. These features are consistent with p53 mutation. As a consequence, expression of p53 protein has been associated with poor clinical outcome and reduced survival in patients, particularly in the younger age group.

CRC patients of all ages are treated at NICRH, but p53 status is not routinely checked and early onset CRC are treated in the same manner as late onset disease. The presence of p53 mutation can have an impact on the effectiveness of both systemic therapy and radiation therapy at various clinical stages.[8][9][10][11][12] Hence, the identification of p53 mutation can aid in the selection of a more appropriate drug regimen, thereby enhancing the chances of survival. The aim of this study was to find out the relative prevalence of p53 protein expression among patients with early- and later onset CRC and analyse other differences in clinicopathological variables among these two subset of CRC patients.

Materials and methods:

Study design: This was a cross sectional study conducted in the Department of Surgical Oncology, National Institute of Cancer Research & Hospital (NICRH), Mohakhali, Dhaka. The study was conducted for a total period of 18 months from 1st October 2021 to 31st March 2023. Patient enrollment was done in first 12 months of the study ensuring a minimum follow up period of at least 6 months for all cases. All patients diagnosed with primary colorectal carcinoma and undergoing curative/palliative resection in Department of Surgical Oncology, NICRH were taken as study sample. Enrolled patients were divided into two groups: (1) Early onset CRC – patients who had their disease diagnosed before the age of 50 years and (2) Later onset CRC – disease diagnosed at or above the age of 50 years. Patients in whom no resection was possible (unfit for surgery/metastatic disease) and those with neuroendocrine tumors or lymphoma of the colon and rectum were excluded from the study. All patients were enrolled after explaining the objective and nature of the study and taking informed written consent.

Tumor samples and Immunohistochemistry: Specimen was preserved in 40% formalin and sent to the Department of Histopathology, NICRH for processing using manual tissue processing technique and paraffin-embedded blocks were prepared. Thin slice sections were cut to prepare slides; two used for H&E staining for histopathology and one preserved for IHC staining for p53 (p53 monoclonal antibody, DO-7 (Roche, Switzerland)). Percentage of p53-positive tumor nuclei in all major foci of cancer were used as p53 IHC scoring system. The percent of p53 immunoreactive tumor cells was scored as 0 to 3+. IHC of p53 protein analysis were grouped as either mutant type (MT - Tumors showing positive phenotype on IHC staining) or wild type (WT - Tumors expressing negative phenotype on IHC staining).

Data collection: Demographic characteristics, clinical and pathological data, operative variables and postoperative outcome variables were collected in a preformed data collection sheet. Histopathology and p53 IHC data were collected and recorded. Patients were advised for follow up at 3 and 6 months after surgery at surgery OPD, with direct telephonic contact if required. All patients were followed up until March 31, 2023 to allow a minimum follow up period of 6 months after surgery. Follow up period was calculated from date of first diagnosis as per patients' records or history.

Statistical analysis: All collected data were entered and analysed with IBM SPSS Statistics 25. Data were compiled, edited, managed and plotted in tabular and figure form. Descriptive statistics, including count and percentage, were used to describe the demographic characteristics of the subjects. The two age groups were compared on different variables using chi square tests, independent t-tests and one way ANOVA. The P-value for significance was set at .05. Survival analysis was expressed using the Kaplan Meier method. The overall survival and disease-free survival rates stratified for single dichotomous prognostic factors were compared between the two age groups using the log-rank test.

Results:

A total of 129 patients, 83 male (64.3%) and 46 female (35.7%) were enrolled in this study. Among them, 75 (58.1%) were early onset CRC and the rest adult onset disease. Mean age was 44.91 ± 13.57 years and female patients were comparatively younger in this study (p=.076). (Table 1) Overall, 35 patients (27.1%) had mutant type p53 expression on IHC analysis. This mutant type p53 expression was more common in younger patients than the elderly patients in this study (34.7% vs 16.7%, p=.018), (Fig. 1). They also had longer duration of symptoms compared to adult onset patients (mean duration 110.93 days vs 86.94 days; p = .008).

Ten patients (7.8%), 6 male and 4 female, gave history of cancer among first/second degree relatives. Incidence of mutant type p53 protein was more in patients with positive family history than those without (70% vs 30.8%, p = .004). In this study, rectum was the primary site in 77 patients (59.7%), followed by right and left colon with 32 (24.8%) and 18 (13.9%) cases respectively). Two patients (1.6%) had synchronous tumors. Although in the younger group a higher percentage of CRCs were right-sided (26.7% vs 10.7%), the difference did not reach statistical significance. Tumor location had no significant association with p53 protein type either. Mean S. CEA level was significantly higher in patients with mutant type p53 protein than those with wild type p53 (6.38 vs 4.25, p=.028).

Histopathology reports of all resected specimen were analyzed and is summarized in Table 2. Four patients showed complete pathological response to neoadjuvant therapy, rest 125 all had adenocarcinoma. Among the younger patients, 35 (48.0%) poor differentiation, mucinous variety or signet ring type, which was significantly more than the elderly group (p=.018). Most of the patients with higher tumor grades were of the younger age group (p=.017). In addition to young age, mutant type p53 protein was also associated with poorer differentiation (p=.035) and higher grade tumors (p < .001).

Lymphovascular invasion (LVI) and perineural invasion (PNI) were more common in MT p53 patients but the differences were not significant. They had no correlation with age groups either.

Seventy five percent patients had either pT2 or pT3 tumors. MTp53 patients had significantly more advanced pT stages (pT3 and above) compared to WTp53 (65% vs 39%; p=.017). MTp53 patients had more number of metastatic lymph nodes (3.17 vs 1.83; .034).

All patients were followed up until March 31, 2023 to allow a minimum follow up period of 6 months after surgery. Follow up period was calculated from date of first diagnosis as per patients' records or history. Mean follow up period was 44.4 ± 15.6 months (Range 8.1-79.7 months). There were thirteen (10.1%) deaths during this period. Those having residual or recurrent (local or distant) were grouped together and were 18 (14.0%) in number. The rest 98 (76.0%) were disease free at end of observation. When analysed against age of onset, it was seen that it had no significant effect on final status of patients in this study (p = .683). Crosstab analysis against p53 mutation showed that percentage of patients remaining disease free at the end of the observation period was significantly less in MTp53 group (60% vs 81.9%). MTp53 patients also had more progression/recurrence (22.9% vs 10.6%) and death (17.1% vs 7.4%) compared to WTp53 patients (p=.035) (Fig. 2). Survival analysis in patients with different p53 status showed that overall survival (OS) and disease free survival (DFS) were both more in wild type p53 than mutant p53 group. For OS, a log rank test was run to determine if there were differences in the survival distribution for the two types of p53 protein (WT/MT). The survival distributions for the two groups were significantly different, $\chi^2(1) = 12.082$, p = .001. Similarly, a log rank test for DFS showed that survival distribution for the two groups were also statistically significantly different, $\chi^2(1) = 13.283$, p < .001 (Fig. 3).

Table-I

Demographic characteristics of the CRC patients (n=129)

Age of disease onset (Years)	Frequency	%	Cumulative %	
< 20	2	1.6	1.6	Early-onset CRC 75 (58.1%)
20-29	16	12.4	14.0	
30-39	25	19.4	33.3	
40-49	32	24.8	58.1	
50-59	29	22.5	80.6	Later-onsetCRC54 (41.9%)
60-69	21	16.3	96.9	
≥70	4	3.1	100.0	
Total	129	100.0		
Mean = 44.91 ± 13.57 years (Male =, Female =)				
Range = 16-90 years				
Gender	n (%)	Mean age	*p*	
Male	83 (64.3%)	46.25 ± 13.51	.076	
Female	46 (35.7%)	42.02 ± 13.36		

Table-II

Immuno-histopathological characteristics (Early vs late onset patients and WT vs MT p53 protein expression)

	Total	Age of onset (years)		*p*	p53 protein expression		*P*
		Less than 50	50 and above		Wild type	Mutant	
Histological type (n=129)				.558			
Adenocarcinoma	125 (96.9%)	73 (97.3%)	52 (2.7%)		92 (97.9%)	33 (94.3%)	
No residual tumor	4 (3.1%)	2 (2.7%)	2 (3.7%)			-	-
Differentiation (n=125)				.018			.035
Well and Moderate differentiation	76 (60.8%)	38 (52.0%)	38 (73.0%)	61 (66.3%)	15 (45.5%)		
Poor differentiation, Mucinous variety & Signet ring type	49 (29.2%)	35 (48.0%)	14 (27.0%)	31 (33.7%)	18 (54.5%)		
Tumor grade (n=125)				.017			<.001
Grade 1	8 (6.4%)	1 (1.4%)	7 (13.5%)		8 (8.7%)	0 (0.0%)	
Grade 2	72 (57.6%)	42 (57.5%)	30 (57.7%)		62 (67.4%)	10 (30.3%)	
Grade 3	45 (36.0%)	30 (41.1%)	15 (28.8%)		22 (23.9%)	23 (69.7%)	
Lymphovascular invasion	79/125 (63.2%)	45/73 (61.6%)	34/52 (65.4%)	.407	55/92 (59.8%)	24/33 (72.7%)	.212
Perineural invasion	29/125 (23.2%)	20/73 (27.4%)	9/52 (17.3%)	.135	17/92 (18.5%)	12/33 (36.4%)	.053
Tumor extension (n=125)							
pT0	4 (3.1%)	2 (2.7%)	2 (3.7%)	.933		-	-
pT1	11 (8.5%)	6 (8.0%)	5 (9.3%)		11 (12.0%)	0 (0.0%)	.011
pT2	54 (41.9%)	31 (41.3%)	23 (2.6%)		44 (47.8%)	10 (30.3%)	
pT3	41 (31.8%)	23 (30.7%)	18 (33.3%)		27 (29.3%)	14 (42.4%)	
pT4	19 (14.7%)	13 (17.3%)	6 (11.1%)		10 (10.9%)	9 (27.3%)	
Lymph node involvement							
Mean total LN harvested	8.67 ± 4.75	8.63 ± 4.75	8.72 ± 4.80	.911	8.18 ± 4.15	9.97 ± 5.95	.057
Mean # of metastatic LN	2.19 ± 3.21	2.24 ± 3.28	2.13 ± 3.14	.848	1.83 ± 2.94	3.17 ± 3.72	.034
pN0	66 (51.2%)	36 (48.0%)	30 (55.6%)	.605	49 (53.3%)	13 (39.4%)	.072
pN1	29 (22.5%)	19 (25.3%)	10 (18.5%)		23 (25.0%)	6 (18.2%)	
pN2	34 (26.4%)	20 (26.7%)	14 (25.9%)		20 (21.7%)	14 (42.4%)	
Pathological stage							
Stage 0	4 (3.1%)	2 (2.7%)	2 (3.7%)	.438	-	-	
Stage I	40 (31.0%)	21 (28.0%)	19 (35.2%)		35 (38.0%)	5(15.2%)	.020
Stage II	19 (14.7%)	11 (14.7%)	8 (14.8%)		11 (12.0%)	8 (24.2%)	
Stage III	54 (41.9%)	31 (41.3%)	23 (42.6%)		40 (43.5%)	14 (42.4%)	
Stage IV	12 (9.3%)	10 (13.3%)	2 (3.7%)		6 (6.5%)	6 (18.2%)	

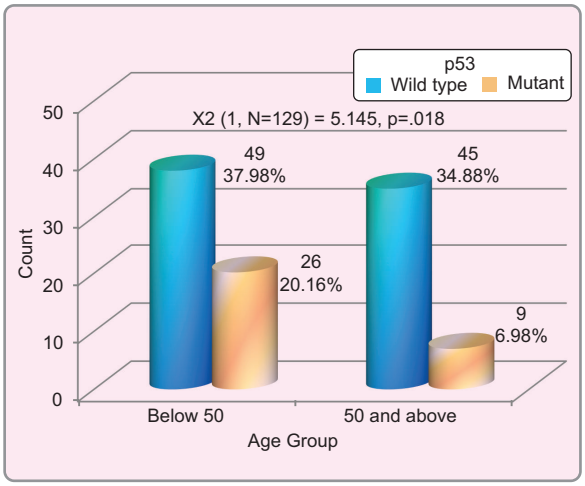

Figure 1: *Distribution of early onset and late onset CRC patients according to p53 protein expression*

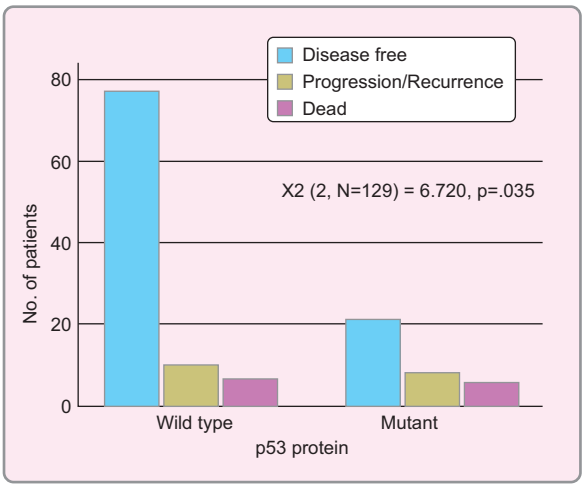

Figure 2: *Distribution of wild type and mutant p53 protein CRC patients according to final outcome at end of study*

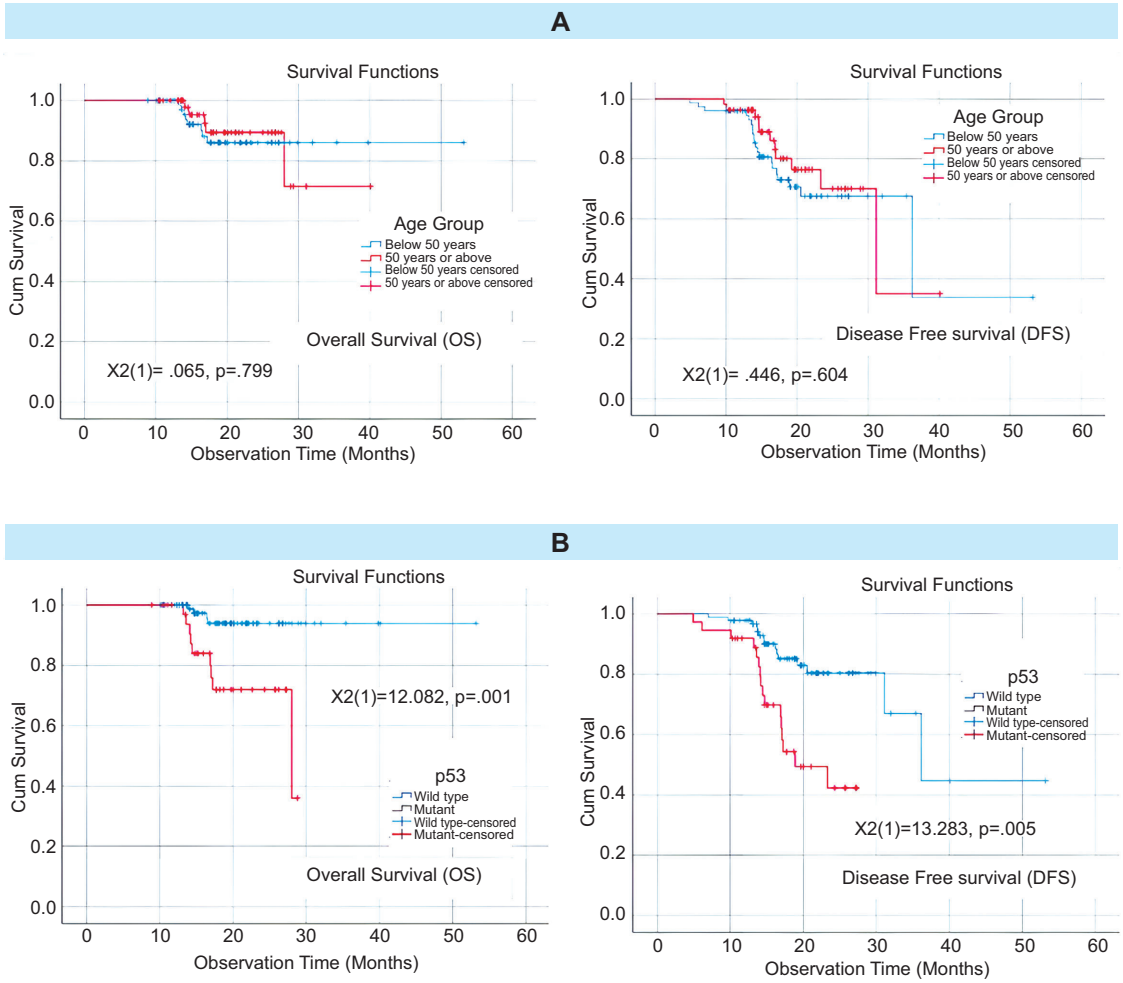

Figure 3: *Kaplan-Meier curves showing probability of survival between (A) early onset and late onset patients and (B) patients with wild type and mutant p53 protein*

Discussion:

Early onset cancer has conventionally been defined as cancer occurring in adults aged between 18 and 49 years. There is a paradigm shift in the ages at which some of the common cancers are being diagnosed[13,14,15]. Researchers worldwide have been working to find relative contributions of both known and unknown risk factors. Mutations of TP53 gene has drawn significant interest in this regard. p53 immunohistochemistry has been widely used as a reliable surrogate test for TP53 mutation status in colorectal and other cancers.[16,17,18] The abnormal/mutant/absent patterns of p53 expression are only indicative of an underlying TP53 gene mutation. This study was designed to find out the differences in p53 protein expression between early and late onset CRC in our department. It also aims to find out how early onset of disease and p53 mutation affects the clinicopathological characteristics of CRC patients.

CRC is traditionally a disease of the elderly: usually presenting in the 5th-7th decades. Patients aged less than 50 years account for 2–8% of all cases.[19] In this study, almost 58% of CRC patients operated upon at NICRH had their disease diagnosed before their age of 50. Mean age of all patients in this study was 44.91 ± 13.57 years (range 16-90), which is significantly lower than that of most other studies (Hoseini et al., 2022 - 55.6 ± 14.8 years, Thomas et al., 2020 - 54.94 ± 11.05 years and Rodriguez et al., 2018 – Median 72 years).[20][21][22] Similar to other studies, there was no significant difference between mean age of male and female patients.[23]

Relatives of individuals diagnosed with early-onset CRC are at a significantly higher risk of developing the disease, emphasizing the importance of earlier screening recommendations.[24] It has been suggested that EO-CRC patients tends to present late with respect to symptom development, which might partly explain the more advanced stage distribution observed at diagnosis.[25,26] Younger patients in our study also had longer duration of symptoms (112.4 vs 88.7 days, p = .032). This could be due to lack of awareness about cancer in early age in both the patients and primary care givers.

Previous researchers reported that early-onset CRCs most commonly occur in the rectum (35-58%), followed by distal colon (25-33%) and proximal colon (8-22%).[4,21,22] This study did not find any significant correlation between tumor location and age groups or p53 mutation. Some authors found predominance of distal colon and rectal tumors in both age groups.[27]

This study found no correlation between age of onset and preoperative serum CEA. But patients with p53 mutation had significantly higher levels of preoperative serum CEA level (p=.028). Park et al also found no difference in percentage of patients with raised CEA levels between the two age groups (35.1 vs 34.2, p=.913).[28] Some authors found no relation between p53 mutation and CEA level,[29] while others have shown significantly raised CEA levels in p53 mutant CRC patients compared to wild type p53 carriers (26.39% vs 9.6%, p=.036).[30]

Early-onset CRC has been associated with certain pathological features such as poor tumor differentiation mucinous variety and signet ring cell formation.[31][32][33] This study also found that early-onset CRC had more chance of unfavorable histologies (poor differentiation, mucinous type and signet ring pathology) as well as higher nuclear grades. Patients with EO-CRC were more likely to be diagnosed at advanced stage (stage III-IV) compared to patients who were diagnosed at a later age.

Prognostic associations of early-onset CRC (compared to later-onset CRC) in the literature show mixed views. Some suggested worse survival among early-onset CRC patients, while others reported similar or even better prognosis. Park et al studied the prognosis of CRC under the age of 50 years. They found similar results in that 5-year OS and DFS were not significantly different (p = .229 and .517 respectively) between the two age groups.[28] Although in their study when the EO-CRC patients were sub grouped at 10-year intervals it was seen that very young patients (below 30 years) had shorter OS and DFS with those below 20 years having 0% survival (p<.001). Liang et al made a stage-by-stage comparison of survival data and showed that younger and older patients with stages I-III had comparable survival data. In contrast younger patients with stage IV disease survived longer than the older patients (cancer-specific survival time 25·46 vs 14·83 months respectively; P<0·001).[34] Another study analysed survival difference between patients below and above 45 years and found no significant difference (Younger group : 5-year OS 61% and median survival 58 ± 6 months; older group : 5-year OS 63% and median survival 63 ± 2 months; p=.738).[27] Rho et al also found no significant difference in mortality analysis between young- and late-onset disease ((for YO: HR, 1.53; 95% CI: 0.91–2.58).[35] Survival analysis in this study didn't show any significant difference in DFS and OS between early- and adult-onset CRC (although both DFS and OS were longer in EO-CRC patients).

From molecular standpoint, CRC as a whole represents a distinctly heterogeneous group of diseases and evidence also indicates molecular heterogeneity in EO-CRC.[36] EO-CRC patients have more p53 mutations and MSI-H tumors, while APC, KRAS, and BRAF mutations are more prevalent in older age group (≥50 years).[37] This study only evaluated p53 mutation and it was significantly more prevalent in the early-onset CRC patients.

Conclusion:

This study indicates that early onset disease was more prevalent than late onset disease among CRC patients operated in NICRH. The younger patients had more mutant type p53 protein on IHC analysis than the elderly. Early age at diagnosis was associated with poor tumor differentiations including mucinous and signet ring type and with higher tumor grades. Age had no association with survival in this study. Mutant p53 IHC was associated with aggressive histology, higher disease stage and poor survival. Findings of this study may help and encourage further studies on early onset colorectal cancer and its association with p53 mutation.

Lack of comprehensive molecular study and long term survival analysis are two notable limitations in this study, but scope remains to carry this work further forward with long term follow up. We recommend meticulous evaluation of younger patients with strong clinical suspicion to exclude EO-CRC and also p53 IHC analysis for every diagnosed patient, particularly the younger age group. We also recommend further studies Involving other departments, notably radiation and medical oncology departments.

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Conflict-of-interest
There is no potential conflict of interest.

Authors' contributions:
Dr. AR was involved in the study design, data collection, data analysis and interpretation and manuscript preparation. Prof. LS was involved in the study design and mentoring. Dr. MAS, Dr. ASAH, Dr. MRA and Dr. MHM were involved in data collection and manuscript preparation. All authors read and approved the final manuscript.

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